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**SUBJECT: DESIGN AND EVALUATION OF AN ALGORITHM FOR
DETECTION OF CARDIAC ISCHEMIA.**

I. EXECUTIVE SUMMARY

An adaptive algorithm for robust detection of cardiac ischemia is described. The algorithm is designed for use with the pseudo-ECG from a subcutaneous electrode array (SEA) in a chronically implanted device. The central operation of the algorithm is measurement of the ST segment with respect to an isoelectric value. The robustness of this operation is vastly improved by adaptive noise detection and by tuning the detection process to rates of ST change that are physiologic during ischemia. The algorithm was tuned empirically based on records from the European ST-T database, a set of 50 two-hour holter recordings with annotated episodes of transient ischemia. Algorithm performance was assessed by receiver operating characteristic (ROC) curves. Compared to the annotated episodes, the algorithm detected ischemia with 80% sensitivity and 80% positive predictivity while requiring only 360 fixed point operations per cardiac cycle (many are simple bit shifts). Some suggestions for future improvements are provided.

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II. ISCHEMIC CHANGES IN THE ELECTROCARDIOGRAM

Cardiac ischemia results in multiple changes in the electrocardiographic waveform, including ST segment elevation or depression, changes in R-wave amplitude, T-wave inversion, increase in Q-T dispersion, and alternans. However, changes in the ST segment are the easiest to detect, are the most recognized and accepted signs of ischemia by physicians, and are likely to be the most sensitive and specific electrocardiographic signs of ischemia.

The physiological basis of ST changes in the presence of cardiac ischemia can be explained by ischemic changes in the action potential of cardiac myocytes (see Figure 1). When myocytes become ischemic, the resting potential increases (toward zero), the depolarization slope of the action potential decreases, the plateau decreases in voltage, and the duration of the action potential decreases. These changes result in voltage gradients and an "injury current" between normal and ischemic myocardium during the resting and plateau phases of the action potential. Because the voltage gradient between the normal and ischemic myocardium is positive during diastole and negative during systole, the isoelectric point and the ST segment of the ECG are displaced in opposite directions during ischemia. Because ECG's are AC coupled, the displacement of the isoelectric baseline is not directly visualized, but the disparity between the isoelectric baseline and the ST segment is easily detected.

III. DESIGN OF THE ALGORITHM

MATLAB code for the ischemia algorithm and a listing of the algorithm variables is presented in Appendix A. The algorithm is designed to process one cardiac cycle for each execution. Auxiliary MATLAB code for loading electrocardiographic signals, parsing the signals into a series of cardiac cycles, and passing the cardiac cycles sequentially to the ischemia algorithm is presented in Appendix B. An array of parameters, representing the state of the ischemia algorithm, is passed back and forth between the ischemia algorithm and auxiliary code. The initial values of the state variables are found in the auxiliary code, and may need to be modified for a given application. Finally, the algorithm listed in Appendix A is not in the most general form; specifically, the code is for an ECG sampled at 125 Hz and 8 bits of resolution, and for 16 bit fixed point processing with 10 bits before the decimal point and 6 bits after (i.e., a parameter resolution of 1/64). The filters contained in the algorithm have been optimized for fixed point processing and all constants are listed with a resolution of 1/64.

The algorithm is best described as a series of five steps. The five steps are roughly processed in order in the MATLAB code, although occasionally they are interspersed. The text below is an overview of the algorithm. For greater detail, see the code in Appendix A.

First Step: Location of Features

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The central fiducial point of each cardiac cycle is the R-wave. The auxiliary code (Appendix B) detects R-waves with a simple bandpass/derivative filter followed by a threshold detector (similar to a pacemaker sense amplifier). Each cardiac cycle is passed to the ischemia algorithm as 16 samples (128ms) before the suprathreshold sample and 40 samples (320ms) after the suprathreshold sample. The ischemia algorithm then determines the locations of 1.) the peak of the R-wave (because the fiducial point is selected based on slope and is not the true peak of the R-wave), 2.) the isoelectric point, and 3.) the ST segment level. These steps are illustrated in Figure 2.

1.) R-wave Peak: The minimum and maximum values are determined within the span of 5 samples (40 ms) before the fiducial point and 7 samples (56 ms) after the fiducial point. A preliminary isoelectric point is selected as the average values of the 8th and 9th samples before the fiducial point. *(Note: averaging over two samples (16 ms) is designed to average over one cycle of 60 or 50 Hz noise, so that the algorithm is relatively indifferent to AC noise).* If the minimum value is further in amplitude from the preliminary isoelectric point than the maximum value, the minimum value is chosen as the R-wave peak. Otherwise, the maximum value is chosen as the R-wave peak. (Because the orientation of SEA electrodes is unknown, the polarity of R-waves is unknown).

2.) Isoelectric Point: Beginning at 5 samples (40ms) before the R-wave peak, the algorithm marches backwards in steps of two samples, searching for a local minimum in the absolute slope between samples. The slope is measured as the absolute difference between two samples that are spaced apart by two samples. The two sample spacing is to avoid measuring the slopes introduced by 60 Hz AC noise. The search concludes when a local minimum of slope is found, or when the search reaches the beginning of the stored ECG segment. The isoelectric point is averaged over 2 samples (16ms).

3.) ST Segment Level: ST segment measurements are conducted at three delays after the R-wave. The delays depend on heart rate; at faster heart rates, the ST segment is closer to the R-wave and is measured over a shorter span. Typical locations for ST segment measurements are at about R+90ms, R+135ms, and R+180ms. At each location, the ST segment is the average over two samples (16ms).

Second Step: Detection of Noise

Noise detection is based on a type of template matching: each cardiac cycle is parameterized by 7 parameters, and these parameters are compared with adaptive expected ranges. If more than 2 of the 7 parameters lies outside of its expected range, the cardiac cycle is rejected as noise. The parameters include: 1.) the R-R interval, 2.) The relative timing of the peak R-waves in the two ECG leads, 3.) The slope of the R-waves, 4.) The noise energy in the isoelectric segment, 5.) the slope of the ST segment, 6.) the difference between the ST and isoelectric values, and 7.) the electrical axis of the R-waves.

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1.) R-R Interval: The R-R interval is measured by the auxiliary code (Appendix B) and is passed as a parameter to the ischemia algorithm. The ischemia algorithm maintains a mean and mean absolute difference (MAD, like a standard deviation but easier to calculate) of the R-R intervals, and determines if the current R-R interval lies within the expected range. Figure 3 is a demonstration of the R-R interval and its expected range. See Step 5 below for an explanation of procedures for when a parameter falls out of range.

2.) Relative Timing of R-Waves: High amplitude noise will likely result in disparate "R-wave" timing between the 2 ECG channels. The timing of the "R-waves" in the two ECG's must be less than 48 ms apart to be accepted. The allowed range was adaptive in a previous version of the algorithm, but is constant in the latest version to reduce computation.

3.) Slope of R-Waves: The slope of each R-wave is calculated as the absolute value of the difference between the first and second samples before the R-wave peak. The actual peak sample is not used because it is not known if this sample is on the rising or falling edge of the R-wave. The slope is calculated separately for each of the two ECG channels, and each slope is compared to an expected range (mean \pm MAD).

4.) Noise in the Isoelectric Segment: This is calculated as the sum of absolute differences between the isoelectric value and 3 samples near the isoelectric value. This absolute number is summed for the two ECG leads and compared to an expected range (mean \pm MAD).

5.) Slope of the ST Segment: The first 2 of the 3 ST segment locations are included in this noise detection parameter. The slope of the ST segment (the difference between the two ST measurements) is compared to an expected range. This is effectively accomplished in 2-D space by making one ECG the x-axis and the other ECG the y-axis.

6.) ST-Isoelectric Value: The sum of the absolute values of the differences between each of the three ST measurements and the isoelectric value is the ST-Isoelectric value. Deviations of the ST-Isoelectric value are used to track ischemia. Instantaneous changes in this value are not consistent with ischemia and are likely to be caused by noise. Therefore, the beat-by-beat ST-Isoelectric value is compared with an expected range. This is also effectively accomplished in 2-D space.

7.) R-Wave Axis: The R-wave amplitudes (R-wave peak - isoelectric value) of the two ECG signals are used to locate the R-wave axis. The location is compared with an expected range of locations. This is accomplished by adding the absolute differences between the 2 R wave amplitudes and their expected means, and comparing this to the expected range.

Figure 4 compares the ischemia parameter when the noise detection aspects of the algorithm are enabled and disabled. The data is from a conscious canine model of cardiac

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ischemia. At the times indicated, a cuff around the LAD is inflated and deflated. The electrocardiogram was obtained from a subcutaneous electrode array (SEA). Clearly, the noise detection circuitry is essential for adequate performance of the device.

Third Step: Calculate the Ischemia Parameter

The basis of the ischemia parameter is the ST-Isoelectric value. For each of the 2 ECG signals, the ST-Isoelectric value is passed consecutively through a series of four lowpass filters. The first filter is a 2nd order Chebychev Type II filter with a relatively high cutoff frequency. This filter is used to detect noisy cardiac cycles, by comparing the instantaneous ST-Isoelectric value with the output of this filter (which is like a running mean). The second filter is a 2nd order Chebychev Type II filter with a cutoff near $\pi/10$. This filter excludes ST changes that occur faster than physiologic ST changes. The filter characteristics were tuned for empirical data of human ischemic ST changes. The third and fourth filters are first order IIR which pass only the lowest frequencies, but are adaptive. Under certain circumstances (such as an axis shift), the slew of their output increases. The outputs of these filters are used to exclude slow drift of the ST segment. In other words, ischemic changes in the ST segment fall in a bandpass region, where changes that are too fast are noise or axis shifts, and changes that are too slow are caused by medication or other forms of baseline drift. Figure 5 demonstrates the outputs of filters 2, 3, and 4. The ischemia parameter is the absolute value of the difference between the outputs of the 2nd and 3rd filters, normalized by the magnitude of the R-wave. When the ischemia parameter is greater than the threshold, the output of the 3rd filter moves toward the output of the 4th filter, which serves as a "home" value of the ST-Isoelectric value.

Fourth Step: Detection of Axis Shifts

Rapid changes in the electrical axis of the heart can cause rapid changes in the ST segment which are not associated with ischemia (see Figure 6, c.f., Adams et al. *J Electrocard.* 1997; 30:285 and Drew et al. *J Electrocard.* 1997; 30(suppl): 157). Such axis shifts are most often caused by a change in posture, but are also possible from sudden onset of blockage in the Perkinje system. Axis shifts are detected by checking for R-wave axis values that are consistently out of range. Specifically, if 18/18, 19/20, 20/22, etc. cardiac cycles have an R-wave axis that is out of range, an axis shift is detected. The detected axis shift causes a form of "reset" of the algorithm. All expected ranges (except for R-R interval) are instantly broadened and allowed to adapt to new values. Figure 7 is an example of how the axis shift detection can avoid false positive ischemia detection.

Fifth Step: Update All Parameters

The seven parameters for noise detection (defined in the Third Step) can be out of the expected range at two different levels ("near" and "far"). The extent that the parameters are out of range affects how the current cardiac cycle is used to update the state variables and expected ranges. As mentioned above, if more than 2 of the 7 parameters are out of the "near" range, the current cardiac cycle is not used to update parameters. Additionally, the individual parameters that are out of the "far" range are not updated by the current cardiac cycle. For example, if the ST-Isoelectric value is within

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the "near" range of mean $\pm 1.6 \times \text{MAD}$, the ST-Isoelectric parameter is not "noisy". If the ST-Isoelectric value is between mean $\pm 1.6 \times \text{MAD}$ and mean $\pm 3.2 \times \text{MAD}$, then the ST-Isoelectric parameter is "noisy" but the current value is used to update the mean and the MAD. If the ST-Isoelectric parameter is outside of mean $\pm 3.2 \times \text{MAD}$, then the ST-Isoelectric parameter and all of the filters that are used to estimate the ischemia parameter are not updated by the current cardiac cycle.

If individual parameters consistently fall outside of the "far" range, e.g., for 12/12, 13/14, 14/16, etc. beats, then the algorithm considers the parameter to have made a step transition to a new state (i.e., a sudden change in rhythm). In this case, the allowed range is forced to expand exponentially (by multiplying MAD by 1.0625 every beat) until the parameter is back into the "near" range. After re-establishing the parameter, the allowed range will slowly shrink to fit the current rhythm. In this way, the algorithm adapts to accept any rhythm from any patient, but is able to reject transient episodes of arrhythmia or noise corruption. An example of this adaptation is highlighted by the arrowhead in Figure 3.

Additional Algorithm Design Notes

- The allowed ranges for each of the parameters was determined empirically from the European ST-T database to be the mean \pm (some multiple of the) MAD.
- The algorithm was originally designed to process two orthogonal ECG signals, and to take advantage of the orthogonality by 2-D processing. However, because 2-D processing requires complicated math operations (like square roots), the algorithm doesn't really operate as a vector electrocardiogram. The two ECG's are considered independent, and their parameters are often added and compared to a single "expected range".
- The slope of the ST segment is not included as part of the ischemia parameter. In an earlier version, the ischemia parameter did include a contribution from ST slope, but this was shown to be of no benefit to algorithm performance.
- The algorithm uses only addition, subtraction, and multiplication as mathematical operations. All divisions are by multiples of 2 and whenever possible, multiplication constants are multiples of 2 to allow easy computation by bit shifts.
- The algorithm typically requires 360 floating point operations per cycle (according to MATLAB "flops" tracking).

IV. EVALUATION OF ALGORITHM PERFORMANCE

Evaluation of algorithm performance was an essential step in the development and testing of the ischemia algorithm, especially because the design of the algorithm was as much empirical as it was theoretical. The evaluation of performance was facilitated by the European ST-T database, which contains 50 two hour holter monitor records, complete with annotated episodes of significant ($>100 \mu\text{V}$) ST deviations. The annotated events were designated by a panel of cardiologists. The 50 records contain a total of 142 annotated ischemia episodes. Two of the 50 records have no annotated episodes. Figure

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8 contains an example of the calculated ischemia parameter and the annotated events for one record in this database.

The basis for performance evaluation was the receiver operating characteristic (ROC) curve, which displays the relationship between algorithm sensitivity and positive predictivity as the ischemia threshold varies. Usually the ROC is a comparison of sensitivity and specificity, where specificity involves the conditional probability of false positives. Because calculation of specificity requires a count of the true negatives, and because true negatives cannot be quantified in this situation, we have substituted positive predictivity for specificity. Positive predictivity is the proportion of detections which were coincident with annotated ischemic events.

The following set of rules were used to determine sensitivity and positive predictivity. The MATLAB code for performance evaluation is listed in Appendix C.

SENSITIVITY If any of the following 3 rules are met, the ischemic event was successfully detected:

- 1.) The ischemia parameter passes above the threshold within 5 minutes of the onset of the annotated ischemic event.
- 2.) The ischemia parameter is above threshold for more than 50% of the duration of the ischemic event.
- 3.) The ischemia parameter is above threshold during the annotated peak ST change of the ischemic event.

POSITIVE PREDICTIVITY If any of the following 3 rules are met, a span of suprathreshold ischemia parameter was associated with an annotated ischemic event:

- 1.) An ischemic event is annotated within the first 300 cardiac cycle period of a suprathreshold ischemia parameter.
- 2.) An ischemic event is annotated for more than 50% of the duration of a suprathreshold ischemia parameter.
- 3.) An ischemic event is annotated during the peak of the ischemia parameter during the duration of a suprathreshold ischemia parameter.

Also, segments of suprathreshold ischemia parameter that were less than 30 seconds apart were combined into one suprathreshold span.

Using these rules, the performance of the ischemia algorithm is presented in Figure 9. As an example, the algorithm achieved about 80% sensitivity and 80% positive predictivity at an ischemia parameter threshold of 0.30. It is important to note that the ischemia algorithm and the expert annotations of the ST database are based on different criteria: annotations on the ST database were based on ST changes of $> 100 \mu\text{V}$, whereas the ischemia algorithm measures ST changes relative to the R-wave amplitude. The threshold of $100 \mu\text{V}$ has no direct correlate to the ischemia parameter. The ischemia algorithm was designed in this manner because $100 \mu\text{V}$ is an arbitrary threshold, and because such an absolute threshold for ST changes would require calibration of any implanted device, and selection of a new arbitrary threshold.

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V. SUGGESTED AREAS FOR IMPROVEMENT

Several areas for improvement in the algorithm exist. Most of these were prompted by investigating algorithm performance on individual records.

- The peak of the R-wave is determined for each cardiac cycle by first finding the local maximum and minimum samples, then detecting a "preliminary" isoelectric point, then selecting which of the minimum or maximum is further in amplitude from the preliminary isoelectric point. This feature was introduced because the orientation of the SEA and the R-waves is unknown. Also, because the SEA may rotate in the pocket or the R-wave axis can shift, the R-wave peak can change orientation. However, this feature is computationally inefficient and the algorithm may often shift between peaks that are of similar amplitudes. For example, if the detected minimum and maximum are nearly the same amplitude away from the preliminary isoelectric point, small changes in wave amplitude can result in a change in the selected peak, and a rapid change in the location of ST segment measurements. This can result in shifts in the ischemia parameter. The phenomenon of shifting R-wave peaks and "jitter" in the location of ST segment measurements has been observed, but the resulting changes in the ischemia parameter have not been significant.
- Wide QRS complexes from conduction blocks or from paced beats may result in incorrect measurement locations for the ST segment and/or the isoelectric point. The algorithm does not adjust the locations of the ST segment or isoelectric point based on the width of the QRS complex.
- The algorithm for location of the isoelectric point can be fooled by wide QRS complexes or QRS complexes with multiple peaks. On one occasion, the algorithm successfully selected the largest peak as the R-wave, but the isoelectric point was located at a prior peak in the wide QRS complex. This occurred because the isoelectric point is at a local minimum in slope between samples, and in this case, the samples spanned the prior peak and the slope between them was near zero.
- Although the ST-Isoelectric filters are tuned to the physiologic rate of ischemic ST changes, there is overlap in the European ST-T database in the rates of nonischemic ST segment drift and the slowest of ischemic ST changes. Therefore, some of the slowly-developing annotated ST changes are interpreted by the algorithm as baseline drift. Perhaps one way to avoid these false negatives is to impose limits for the amplitude of drift. The expert annotations regard any change of $> 100 \mu\text{V}$ as ischemia, regardless of the cause. The algorithm, however, does not hold any "absolutes" in the ST deviation. Any level of ST-Isoelectric is acceptable, so long as level changes occur slowly enough. I would propose either 1.) imposing absolute limits for how much the ST segment can drift from the isoelectric point, or 2.) Keep 10 measurements of the ST-Isoelectric parameter in memory, one measurement each minute. The difference in the first and last measurements in this rolling buffer must not be greater than an absolute limit.
- Computation might be reduced without degrading performance by reducing the number of parameters used for noise detection.

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- For a consistently out of range parameter to be called a new rhythm, should be a consistent direction of error: i.e., always much greater or much less than the current mean value. If sometimes greater and sometimes less than allowed range => total noise.

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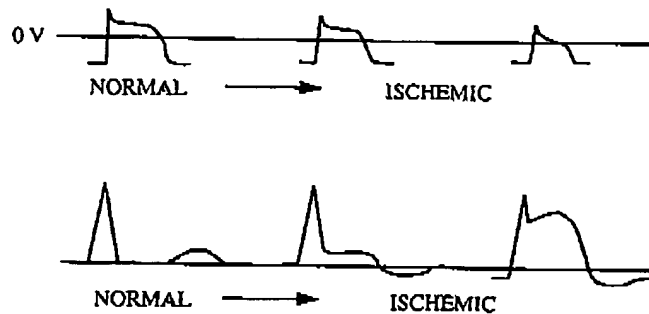


Figure 1: Top: A diagram of the changes in cardiac myocyte action potential that result from ischemia. Ischemia decreases the activity of ion pumps, which changes the resting potential, action potential, and propagation velocity of the ischemic cells. Bottom: The corresponding changes in surface ECG. Voltage differences between ischemic and normal tissue cause the flow of "injury current". The voltage differences change the baseline and ST segment levels of the ECG.

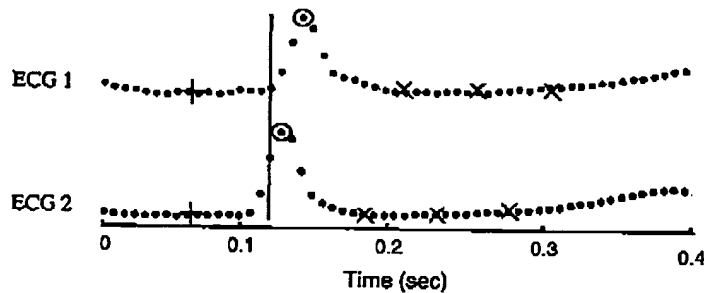


Figure 2: Location of features in the ECG. The dotted lines are the samples of the two channel ECG that are passed to the ischemia algorithm for each cardiac cycle. The solid vertical line is the fiducial point (sense amp. detection of R-wave). The circles indicate the selected peaks of the R-waves, the '+'s indicate the isoelectric points, and the 'X's indicate the ST segment measurements. The isoelectric point and the ST segment measurements are each averaged over two samples (16ms) to reduce the effects of AC noise.

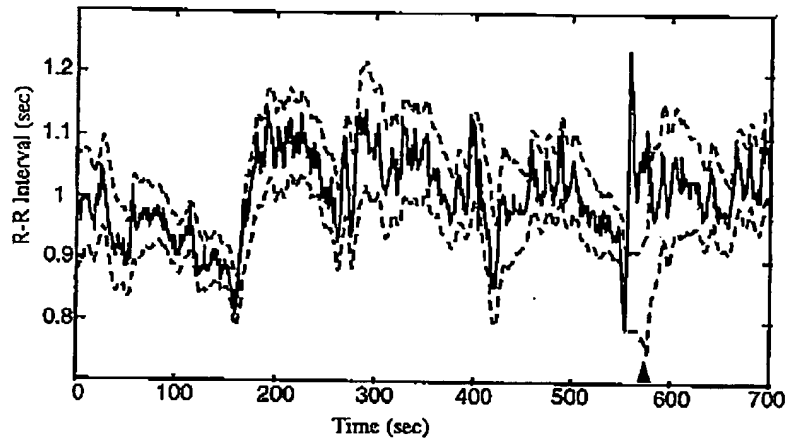


Figure 3: Comparison of the R-R interval (solid line) to its expected range (mean \pm 3*MAD, dashed lines). At about 550 seconds, the R-R interval passes well outside of the expected range for an extended duration. The expected range remains steady for 12 cardiac cycles, waiting for the "noise" to end. At this point, the algorithm decides that a new "normal" has developed and adapts (arrowhead) to accept the new normal.

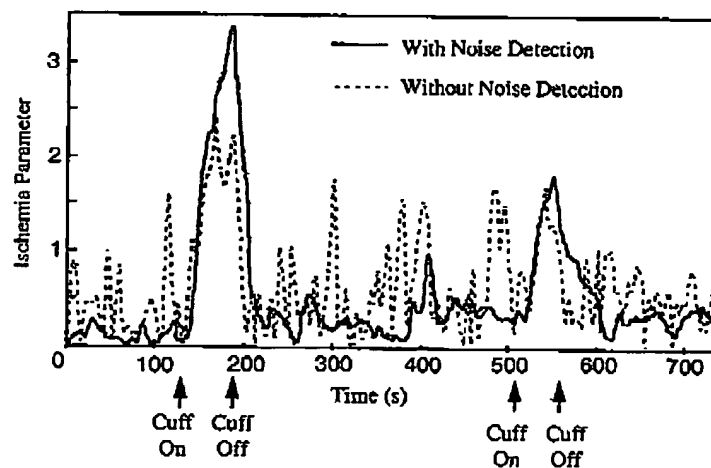


Figure 4: A demonstration of the benefit of the noise detection portion of the algorithm. The dashed line is the ischemia parameter as calculated with the noise detection aspects of the algorithm disabled. The solid line is the result with noise detection intact. The data is from a conscious canine model of cardiac ischemia. A cuff around the LAD is inflated and deflated at the times indicated.

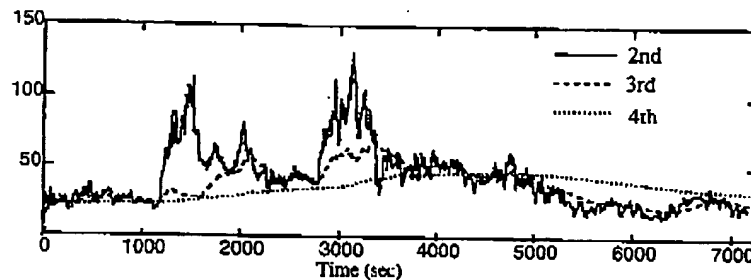


Figure 5: Determination of the ischemia parameter. The raw ST-Isoelectric signal is passed through a series of four lowpass filters. The first filter is used to detect instantaneous changes in the ST-Isoelectric value that are consistent with noise. The outputs of the 2nd through 4th filters are shown in the figure. The 2nd filter is tuned to the observed rate of ST change during ischemia. The output of the 3rd filter follows slow drift of ST change. Ischemic changes are superimposed on this slow drift. The output of the 4th filter changes very slowly with the ST baseline. This output serves as a "home" value. When ischemia is detected, the output of the 3rd filter moves toward the "home" value. The ischemia parameter is the 2-D distance between the outputs of the 2nd and 3rd filters, normalized by the magnitude of the R-wave.

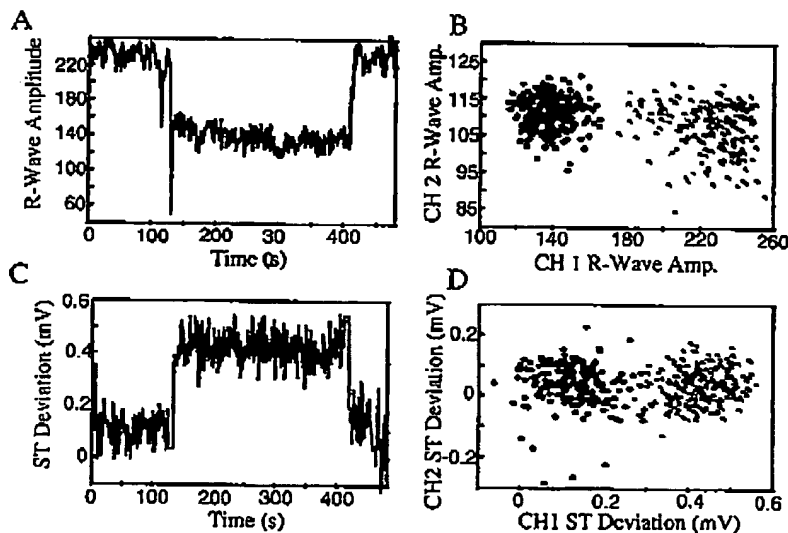


Figure 6: A.) A rapid change in R-wave amplitude, presumably caused by a change in postural position. B.) The axis shift is evident by a 2-D plot of R-wave amplitudes. C.) Corresponding change in ST deviation from the isoelectric level. D.) The axis shift caused a re-location of the 2-D ST-Isoelectric vector.

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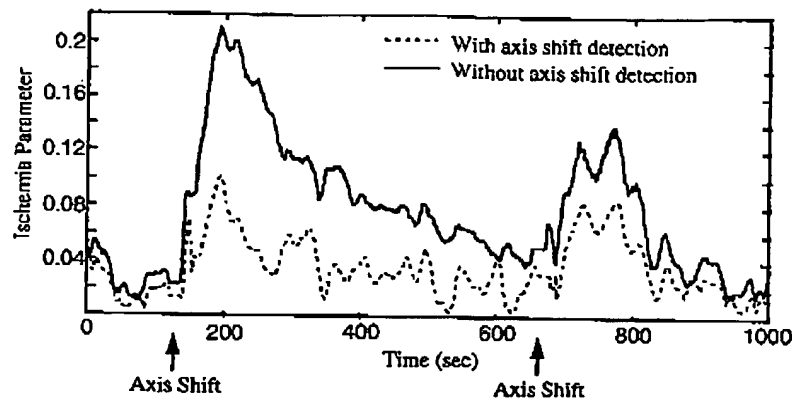


Figure 7: Correct axis shift detection reduces the effects of axis shifts on the ischemia parameter. After an axis shift is detected, the range of accepted parameter values is expanded and the ST-Isoelectric baseline adapts to the new level.

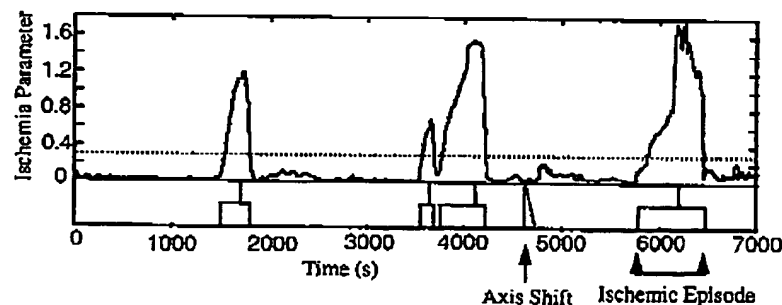


Figure 8: The ischemia parameter (the output of the ischemia algorithm) for one record of the European ST-T database. The boxes indicate the annotated ST changes, the lines on top of the boxes indicate the annotated time of the peak ST change, and the triangle indicates an axis shift as detected by the ischemia algorithm (axis shifts are not annotated in the database). The dotted line indicates a common threshold for the ischemia parameter (0.3).

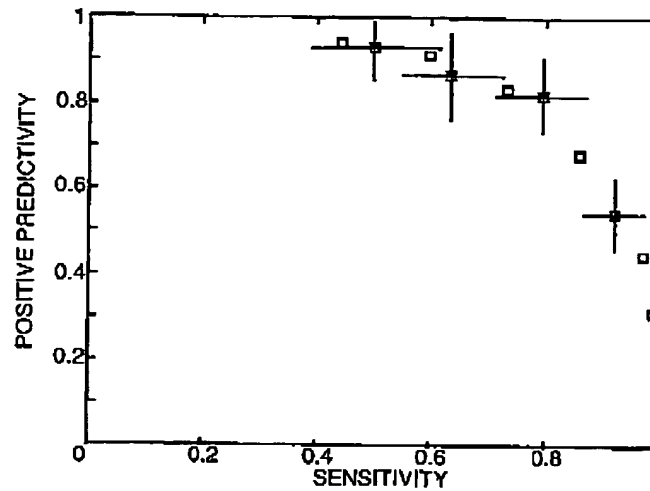


Figure 9: The performance of the ischemia algorithm relative to the expert annotations in the European ST-T database. Beginning at the bottom right and progressing to the upper left of the panel, the ischemia parameter threshold is 0.05 to 0.60 in steps of 0.05. The vertical and horizontal lines are representative 95% confidence intervals.